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Myeloid leukemia factor

A return ticket from human leukemia to fly hematopoiesis

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Even though deregulation of human MLF1, the founding member of the Myeloid Leukemia Factor family, has been associated with acute myeloid leukemia, the function and mode of action of this family of genes have remained rather mysterious. Yet, recent findings in Drosophila shed new light on their biological activity and suggest that they play an important role in hematopoiesis and leukemia, notably by regulating the stability of RUNX transcription factors, another family of conserved proteins with prominent roles in normal and malignant blood cell development.

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Myeloid Leukemia Factors

One hallmark of leukemic blood cells is the presence of recurrent chromosomal rearrangements that play a critical role in malignancy by disrupting the activity of the gene(s) they affect. Accordingly, the cloning of translocation breakpoints has been instrumental for defining the molecular basis of cell transformation as well as for identifying new genes implicated in hematopoiesis. In 1996, the molecular characterization of a rare chromosomal rearrangement associated with acute myeloid leukemia (AML), led to the discovery of myelodysplasia/myeloid leukemia factor 1 (hMLF1),[1] the founding member of a family of proteins found in all metazoans.[2] Whereas two paralogs (MLF1 and MLF2) sharing around 40% of identity are present in vertebrates, a single MLF is found in lower species such as Drosophila (**Fig. 1**). *MLF* genes code for small (± 270 amino acids) nucleo-cytoplasmic shuttling proteins characterized by a conserved central domain devoid of particular structural feature.[3,4] Except for a consensus binding motif to the 14-3-3 family of adaptor proteins, they show no homology with other known proteins, suggesting that they function through a novel pathway. Below, we summarize our current knowledge of MLF functions and we discuss the unanticipated link between MLF and members of the RUNX transcription factor family during normal and pathological development.

MLF in Leukemia

hMLF1 was identified as a target of the t(3;5)(q25.1;q34) translocation in patients with myelodysplastic syndrome (MDS) or AML. The t(3;5) translocation produces a fusion protein between the N-terminal domain of Nucleophosmin (NPM1), a previously characterized multifunctional nucleolar protein, and almost the entire hMLF1 (**Fig. 1**). NPM1 N-terminal domain is also found in other chimera associated with AML[5] and is believed to act by providing a domain of oligomerization and nuclear localization that converts its fusion partners into oncoproteins. Accordingly, NPM-MLF1 is observed principally in the nucleus both upon transfection or in primary t(3;5)-positive MDS/AML samples, whereas hMLF1 is mainly cytoplasmic.[1,6] Consistent with a direct role in blood cell malignancy, NPM-MLF1 expression enhances murine hematopoietic progenitor proliferative potential in vitro, and it facilitates escape from senescence or RasV12-induced oncogenic transformation in mouse embryonic fibroblast.[7]

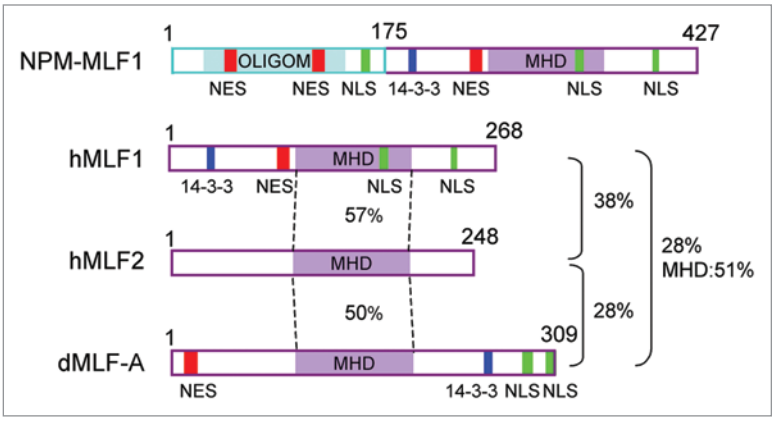

Figure 1. Schematic representation of MLF family members in human and Drosophila. The fusion protein NPM-MLF1 produced by the t(3;5) translocation consists of the N-terminal region of NPM1 (amino acids 1 to 175) fused to the almost entire hMLF1 (amino acids 16 to 268). In Drosophila, four isoforms of MLF with different N or C-terminal regions are generated by alternative splicing. The best studied isoform is dMLF-A (schematized here). The various domains identified in these proteins are depicted. NES: nuclear export signal. NLS: nuclear localization signal. OLIGOM: NPM1 oligomerization domain. 14-3-3: consensus binding motif for 14-3-3 proteins. MHD, MLF homology domain. The percentage of identify between MLF proteins or their MHD regions are indicated.

Of note, disruption of one *NPM1* allele was also proposed to play a role in t(3;5)-associated leukemogenesis.[8] Indeed, NPM1 is a critical regulator of hematopoiesis and point mutations causing its aberrant cytoplasmic accumulation are frequently found in AML.[5] Intriguingly, some wild type NPM1 protein is mislocalized in t(3,5)$^{+}$ AML cells[6] and, although NPM-MLF expression alone is not sufficient to induce NPM1 accumulation in the cytoplasm, altered NPM1 function may be involved in t(3;5)-induced blood cell transformation.

By bringing *hMLF1* under the control of *NPM1* 5' regulatory sequences, the t(3,5) translocation also deregulates the expression of *hMLF1*, which is normally observed in hematopoietic progenitors and decreases during blood cell differentiation.[9] Whereas the wild type copy of *hMLF1* is not detectably expressed in t(3;5)-positive MDS/AML blood cells, *NPM-MLF1* expression is observed both in immature erythroid cells and in myeloid blasts.[1,6] Therefore, NPM-MLF1 oncogenic activity may be linked to MLF1 overexpression. Accordingly, higher levels of *hMLF1* correlate with poor prognosis AML and with malignant progression from MDS in t(3;5)-negative patients, suggesting that increased hMLF1 expression disrupts hematopoiesis and favors blood cell transformation.[9] Nonetheless, the causal role of NPM-MLF1 and hMLF1 in MDS and AML onset has not been demonstrated yet.

MLF Functions in Mammals

In mouse, *mMLF1,* which is 80% identical to *hMLF1* at the protein level, was originally cloned as a gene upregulated during the conversion of an erythroleukemic cell line into myeloid cells, a lineage-switch process that involves the reprogramming of committed cells.[10] Indeed, enforced expression of mMLF1 is sufficient to inhibit erythroid differentiation and to promote myeloid differentiation both in leukemic and primary blood cells.[10] Further analysis in erythroleukemic cells showed that mMLF1 interferes with erythroid differentiation by promoting the degradation of the cell cycle inhibitor p27^{Kip1}, thus preventing cell cycle exit.[11] In contrast, hMLF1 overexpression induces cell cycle arrest in a p53-dependent manner in different cell lines and in primary mouse fibroblasts.[12] At the molecular level, hMLF1 induces the accumulation of this tumor suppressor by binding the COP9 signalosome component CSN3 thereby downregulating the p53 E3 ubiquitin ligase COP1.[12] Unlike hMLF1, NPM-MLF1 does not activate p53 but rather seems to antagonize its induction by various stresses.[7]

Interestingly, mutation of hMLF1 nuclear export signal increases its antiproliferative activity and impedes NPM-MLF1 oncogenic potential, indicating that nucleo-cytoplasmic shuttling of hMLF1 plays a critical role in regulating its function and could control the oncogenic conversion of hematopoietic cells.[7] Along this line, it is worth noting that human and mouse MLF1 exogenously expressed in COS7 or NIH3T3 cells are predominantly cytoplasmic, whereas endogenous mMLF1 is observed mainly in the nucleus of erythroleukemic and monoblastoid cell lines.[4] Thus, the effect of MLF on cell cycle may not only depend on p53 status but also on its subcellular localization. Actually, three partners of mMLF1 have been proposed to regulate its localization: hnRNP-U-L2/MANP (MLF1-associated nuclear protein) favors its nuclear accumulation whereas the adaptor NRBP1/MADM (MLF1-associated molecule) and the phosphoserine binding protein 14-3-3-zeta could participate in the cytoplasmic retention of mMLF1 phosphorylated by a yet unknown MADM-associated kinase.[4,13] However, the role of these different proteins in vivo and their contribution to MLF1 function have not been addressed. Finally, MLF proteins have been shown to interact with a handful of other proteins such as the centromere component MLF1IP/CENP-U[14] or the transcription factors RFX4[15] but, again, these interactions were not further studied.

Altogether, in the absence of knock out or knock down experiments, the developmental and physiological roles of MLF proteins in mammals remain poorly characterized.

MLF Functions: Insights from Drosophila

The presence of a single *MLF* gene in the Drosophila genome and the availability of numerous genetic tools raised hopes that this model organism would bring valuable information about MLF family members. dMLF was initially identified as a partner of DREF (DNA Replication Enhancer Factor),[3] a transcription factor that regulates the expression of genes involved in proliferation. Furthermore,

dMLF binds to Drosophila and mouse Su(Fu), an inhibitor of Hedgehog (Hh) signaling implicated in the regulation of the Ci/Gli transcription factors activity.[16] Unlike hMLF1, dMLF is mainly nuclear but its nucleo/cytoplasmic repartition varies in different tissues.[2] Notably, dMLF accumulates in the nucleus of differentiating cells while it is also cytoplasmic in proliferating tissues.[2] Structure/function analysis in cell culture revealed that dMLF contains two nuclear localization signal as well as a potential nuclear export signal (**Fig. 1**).[17] Also, among the 4 dMLF isoforms generated by alternative splicing, one of them (dMLFB) lacks the C-terminal region containing the nuclear localization signals.[2,17] In line with a role in controlling cell proliferation, dMLF overexpression induces severe developmental defects accompanied by both cell death and increased DNA synthesis.[2] Genetic interaction experiments suggest that some of these defects could be linked either to DREF, Su(Fu) or CSN3 deregulation.[16,18] In addition, works in fly suggested that MLF might have a neuroprotective activity. Indeed, dMLF overexpression inhibits polyglutamine-induced toxicity in different fly models of neurodegenerative disorders.[2,19] Strikingly, this function seems conserved: both hMLF1 and hMLF2 reduces poly-Q toxicity in fly, whereas human and Drosophila MLF suppress poly-Q toxicity in primary rat neuronal cultures.[2,20] Intriguingly, hMLF1 overexpression in mouse skeletal muscle generate intracellular aggregates, even though their accumulation did not seem pathogenic.[21] Thus, the exact role of MLF in neurodegenerative disorders is still elusive.

dMLF in Hematopoiesis

Disappointingly, the generation of *dmlf* null mutant alleles did not bring much information about its function initially: most mutants die during embryogenesis without obvious defects and the few emerging adults are fertile and only exhibit subtle phenotypes.[2] Yet, three independent studies pointed toward a possible role for *dmlf* in hematopoiesis. First, *dmlf* expression pattern suggested that it is expressed in the crystal cells, one of the three main blood cell lineages in Drosophila.[2] Second, *dmlf* was identified as a putative direct target of the RUNX transcription factor Lozenge (LZ), which is crucial for the development of this particular lineage.[22] Third, in a genome wide RNAi screen, dMLF scored as a potential co-activator of LZ.[23] Further analysis revealed that *mlf* participates in a positive feedback loop to control the activity of LZ.[24] Indeed, dMLF expression is activated in the crystal cell lineage by LZ and required for stabilizing LZ, thereby contributing to the fine-tuning of crystal cell number. In addition to this lineage-specific function, dMLF participates in the maintenance of larval blood cell progenitors in their quiescent and undifferentiated state: in the absence of *dmlf* the Drosophila larval hematopoietic organ is overgrown and the population of blood cell progenitors greatly reduced.[24] Since Hh signaling is required for progenitor maintenance[25] and mutations in the COP9 signalosome have been associated with blood cell hyperproliferation,[26] dMLF may regulate blood cell progenitor fate by targeting either of these pathways. These data highlight the critical roles of dMLF during hematopoiesis in vivo. Given the strong conservation of the genetic network controlling blood cell development from fly to humans,[27] it is likely that these findings in Drosophila will find some echo in mammals.

MLF: A Conserved Regulator of RUNX Transcription Factors Stability

Strikingly, expressing hMLF1 is sufficient to restore both normal crystal cell number and LZ expression in a *dmlf* mutant background, suggesting that the regulation of RUNX protein stability by dMLF has been conserved through evolution.[24] In mammals, the three *RUNX* genes play prominent roles in the development of different tissues.[28] Notably, *RUNX1/AML1* is required at several steps of blood cell development, from hematopoietic stem cell emergence to differentiation into T cells or megakaryocytes. Moreover, mutations affecting *RUNX1* are frequently associated with blood cell malignancies. For instance, the t(8;21) translocation, which generates the RUNX1-ETO fusion protein, is responsible for 12% of all cases of AML. Remarkably, dMLF also stabilizes RUNX1-ETO and is required for its activity in vivo in a Drosophila model of leukemia.[24] Moreover, knocking-down hMLF1 impairs RUNX1-ETO accumulation and reduces RUNX1-ETO-dependent proliferation in a human leukemic cell line. LZ and RUNX1-ETO only share homology through their DNA-binding domain, which characterizes all RUNX family members. Hence, even though it has not been demonstrated that all RUNX family members are regulated by MLF, the control of RUNX protein level appears as a conserved feature of MLF proteins.

At the molecular level, MLF seems to protect RUNX transcription factor from degradation by the proteasome.[24] Several non-exclusive hypotheses could explain this protective effect. First, MLF protein could favor the interaction between RUNX and their cofactor CBFß, which is required to prevent RUNX degradation by the proteasome.[29] Second, since hMLF1 inhibits CSN3/COP9-induced degradation of p53 and CSN5 stimulates RUNX3 degradation,[12,30] MLF may protect RUNX via this pathway. Third, MLF may regulate SCF ubiquitin ligase complex by targeting Su(Fu).[16] Interestingly, loss of dMLF in the eye only resulted in a slight downregulation of LZ levels, suggesting that the regulation of LZ stability is tissue specific.[24] Post-transcriptional modifications of RUNX proteins have been implicated in the regulation of their turnover[28] and MLF could impinge on these modifications. Alternatively, MLF may stabilize RUNX proteins by promoting their association with chromatin or their nuclear import. Also, since dMLF binds discrete foci on chromatin,[16] it is tempting to speculate that it may have a direct role in regulating the transcriptional response to LZ and other transcription factors.

Importantly, deregulation of RUNX protein level has been associated with different pathologies in humans.[28] Haploinsufficient mutations in *RUNX1* are found in patients with familial platelet disorders and propensity to develop AML. Conversely, increased *RUNX1*

dosage has been proposed to participate in blood cell transformation, notably in patients with Down syndrome. Similarly, increased or decreased expression of *RUNX2* is respectively associated with T-cell lymphoma in mouse and cleidocranial dysplasia in humans, while reduced *RUNX3* levels are linked to gastric cancer. Hence, a tight regulation of RUNX protein level is crucial for proper development. Also, RUNX proteins can behave either as tumor suppressors or oncogenes, depending on the cellular context.[28] MLF proteins may have a similar behavior and it will be of particular interest to study the relationship between MLF and RUNX in AML as well as in other cancers.

Concluding Remarks

In conclusion, recent studies point toward an important function of MLF in the control of blood cell development notably by regulating RUNX transcription factors activity. The striking conservation of the core regulatory network controlling hematopoiesis from human to fly and of MLF function in these organisms provides a worthy framework to study MLF using Drosophila as a model organism. Deciphering how MLF controls RUNX stability will not only bring new light on MLF but also on RUNX regulation, which is critical for the homeostasis of several tissues. However, RUNX are certainly not the only targets of MLF proteins. We anticipate that the combination of genetic and biochemical assays will help obtain a comprehensive understanding of the physiological roles and molecular mechanisms of action of this peculiar family of proteins.

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